REMARKS

Claims 1-35 are currently pending in the application. Claim 31 has been amended. Support for the amendment is found throughout the specification, for example on page 3, lines 17-19. Applicants respectfully assert that no new matter has been added and request reconsideration of the claims currently pending in the application.

Applicants' representative filed a Revocation and Power of Attorney with Statement Under 37 C.F.R. § 3.73 (b) on April 9, 2003. To date, Applicants have not received any notification of acceptance of power of attorney. The Official Action mailed October 3, 2003 was sent to Applicants' previous representative. Copies of relevant documents regarding this matter and the return post card having a Patent and Trademark Office date stamp of April 17, 2003 are enclosed in this response as Exhibit A. It is respectfully requested that the Office records be updated.

I. Rejection based on 35 U.S.C. §102

1. On page 2 of the Office Action, claims 31-35 are rejected under 35 U.S.C. §102 (b) as being anticipated by Carlyle, et al. (WO 99/37337).

The Examiner notes that Carlyle et. al. teach a substrate on which is coated VEGF or related factors, which are attached via chemical bonding, crosslinking or an adhesive, and thus anticipates the claim subject matter.

The Applicants respectfully traverse the rejection.

The Applicants agree that Carlyle et. al. teach a substrate on which is coated VEGF or related factors, which are attached via chemical bonding, crosslinking or an adhesive. Carlyle et. al. broadly teach the association of growth factors with substrates to stimulate cell growth. However, as is clearly disclosed in the present invention, stimulating compounds are not growth factors, but compounds that stimulate the production of growth factors including VEGF. See page 2, lines 26-27, and page 13, lines 19-26. The specific teaching and examples in Carlyle et. al. concentrate on the attachment of already isolated growth factors onto the substrates, while the subject matter of claim 31 is directed to the method of associating a biomaterial with a stimulation compound to stimulate the growth of growth factors such as VEGF on the medical device, which in turn stimulates the growth of cells. This method is not specifically exemplified nor mentioned in Carlyle et. al. Thus, the subject matter of claim 31 is different from the broad teachings of Carlyle et. al.

To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Therefore, all claim elements, and their limitations, must be found in the prior art reference to maintain a rejection based on 35 U.S.C. §102. Applicants respectfully submit that Carlyle et. al. does not teach every element of claim 31, and therefore fails to anticipate claim 31.

Dependent claims 32-35, which are dependent from independent claim 1, were also rejected under 35 U.S.C. §102(b) as being unpatentable over Carlyle et. al. While Applicants do not acquiesce with the particular rejections to these dependent claims, it is believed that these rejections are moot in view of the remarks made in connection with independent claim 1. These dependent claims include all of the limitations of the base claim and any intervening claims, and recite additional features which further distinguish these claims from the cited references. Therefore, dependent claims 32-35 are also in condition for allowance.

Applicants respectfully request withdrawal of the rejection of claims 31-35 under 35 U.S.C. §102 (b) as being anticipated by Carlyle, et al.

2. On page 2 of the Office Action, claims 31-33 are rejected under 35 U.S.C. §102 (b) as being anticipated by Keogh (U.S. Patent Number 6,033,719).

The Examiner notes that Keogh teaches a device on which is coated a biomolecule factor through covalent bonds and thus anticipates claims 31-33.

Applicants respectfully traverse the rejections.

Keogh discloses improved methods for covalently attaching a biomolecule to a substrate surface, and specifically, to covalently immobilize at least one biomolecule on the surface of a biomaterial. See col. 2, lines 30-34. The biomolecule comprises a 1, 2 dicarbonyl moiety for covalently bonding to such biomaterial surfaces comprising guanidino moieties. See col. 3, lines 56-59. A long list of biomolecules are disclosed, including a growth factor, a nucleic acid, a DNA segment, RNA segment, a drug and so on, provided it has the required 1, 2 dicarbonyl moiety for covalently bonding to

biomaterial surfaces comprising guanidino moieties. See col. 6, lines 22-56. Thus, Keogh teaches the selection from the universe of biomolecules of ones having a 1, 2 dicarbonyl moiety. It does not teach a stimulation compound for stimulating the growth of growth factors. In addition, stimulation compounds do not necessarily have to comprise a 1, 2 dicarbonyl. Thus, the selection in Keogh from the broad range of biomolecules of ones fitting the criteria is related to a different invention than that disclosed in claim 31. Therefore Keogh does not anticipate the subject matter of claim 31.

Claims 32-33, which are dependent from independent claim 1, were also rejected under 35 U.S.C. §102(b) as being unpatentable over Keogh. While Applicants do not acquiesce with the particular rejections to these dependent claims, it is believed that these rejections are moot in view of the remarks made in connection with independent claim 1. Therefore, dependent claims 32-35 are also in condition for allowance.

Applicants respectfully request withdrawal of the rejection of claims 31-33 under 35 U.S.C. §102 (b) as being anticipated by Keogh.

3. On page 3 of the Office Action, claims 1-2, 7, 23-24, 26, 28, 31-33, and 35 are rejected under 35 U.S.C. §102 (b) as being anticipated by Martin, et al. (WO 98/20027).

The Examiner notes that Martin, et al. teach a device onto or into which a VEGF agonsit is attached (see for examples the claims), and therefore anticipates claims 1-2, 7, 23-24, 26, 28, 31-33, and 35.

Applicants respectfully traverse the rejections.

Martin, et al. discloses a therapeutic use of growth factors. See page 1, lines 4-6. They find that VEGF is capable of suppressing intimal hyperplasia in situations where intimal hyperglasia arises when the endothelium is wholly or largely intact, and thus potentially capable of preventing or treating de novo stenosis. See page 4, lines 25-29. Therefore, Martin, et al. teach the inhibition of hyperplasia. See page 5, lines 14-19, and 24-28. In addition, Martin, et al. teach that VEGF agonists can be used in practicing their invention. See page 10, line 22 to page 13, line 17. An agonist, as noted in Martin, et al., is a molecule which binds to a receptor to which VEGF normally binds, and has substantially the same effects as a VEGF would have. See page 10, lines 25-26. Thus, a VEGF agonist functions like a VEGF and takes the place of VEGF.

On the other hand, the subject matter of claims 1 and 31 is directed to a stimulation compound that stimulates the production of growth factors like VEGF. This is different than the teaching of Martin, et al., which is directed to VEGF or its agonists for use in suppressing intimal hyperplasia in situations where intimal hyperglasia arises when the endothelium is wholly or largely intact, and thus potentially capable of preventing or treating de novo stenosis. Since Martin, et al. teach a different invention, they do not teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Therefore, Martin, et al. fails to anticipate claims 1 and 31.

Claims 2, 7, 23-24, 26, 28, 32-33, and 35, which are dependent from independent claims 1 and 31, respectively, were also rejected under 35 U.S.C. §102(b) as being unpatentable over Martin, et al. While Applicants do not acquiesce with the particular rejections to these dependent claims, it is believed that these rejections are moot in view of the remarks made in connection with independent claims 1 and 31. Therefore, dependent claims 2, 7, 23-24, 26, 28, 32-33, and 35 are also in condition for allowance.

Applicants respectfully request withdrawal of the rejection of claims 1-2, 7, 23-24, 26, 28, 31-33, and 35 under 35 U.S.C. §102 (b) as being anticipated by Martin, et al.

4. On page 3 of the Office Action, claims 31-33 are rejected under 35 U.S.C.§102 (a) as being anticipated by Slaikeu, et al. (WO 01/03607).

The Examiner notes that Slaikeu, et al. teach a medical device on which is coatedor associated an angiogenic factor and thus anticipates claims 31-33.

Applicants respectfully traverse the rejections.

Slaikeu, et al. disclose a stent coated with a composition having an angiogenic response. See page 7, lines 13-23. A long list of angiogenic factors including a growth factor, a nucleic acid, a pharmaceutically active compound and so on, is listed, as long as it produces the required angiogenic response. See page 11, line 8, to page 13, line 29. There is no teaching of how to associate a stimulation compound with a biocompatible material that stimulates the production of growth factors, the subject matter of claim 31. Slaikeu, et al. teach a different invention and therefore do not anticipate claim 31 because they do not teach every element of the claim. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The

identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Therefore, Slaikeu, et al. fail as a reference for sustaining a rejection based on 35 U.S.C. §102 (a).

Claims 32-33, which are dependent from independent claim 31, were also rejected under 35 U.S.C. §102(a) as being unpatentable over Slaikeu, et al. While Applicants do not acquiesce with the particular rejections to these dependent claims, it is believed that these rejections are moot in view of the remarks made in connection with independent claim 31 and are also in condition for allowance.

Applicants respectfully request withdrawal of the rejection of claims 31-33 are rejected under 35 U.S.C. §102 (a) as being anticipated by Slaikeu, et al.

II. Rejection based on 35 U.S.C. § 103(a)

1. On page 4 of the Office Action, claims 1-35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Carlyle, et al. in view of Martin, et al.

The Examiner notes that Carlyle et. al. teach a needed medical device on to which VEGF has been attached to promote population of the device with viable cells and other positive results, and thus Carlyle et. al. teach all of the claimed devices in detail through the reference and also details means for attaching the peptide to the device in all the methods Applicants' claim. The Examiner also notes that Carlyle et. al. use VFGF, though does not teach using a VEGF stimulation compound, but adds that at the time the invention was made it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute a VEGF stimulation compound for the VEGF used by Carlyle et. al. because Martin teaches that using such compounds produces like

results to using the peptide itself, and therefore the references clearly provide a reasonable expectation of success that using known stimulator/agonist of VEGF on a medical device would produce the same desired results as sought by et. al. The Examiner further notes that as the references clearly indicate that the various proportions and amounts of the ingredients used in the claimed device are result effective variables, they would be routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by those references.

Applicants respectfully traverse the rejections.

As noted above, Applicants agree with the Examiner that Carlyle et. al. use VFGF, but does not teach using a VEGF stimulation compound. However, as is clearly disclosed in the present invention, stimulating compounds are not growth factors, but compounds that stimulate the production of growth factors including VEGF. See page 2, lines 26-27, and page 13, lines 19-26. Carlyle et. al. broadly teach the association of growth factors with substrates to stimulate cell growth. The specific teaching and examples in Carlyle et. al. concentrate on the attachment of isolated growth factors onto the substrates, as noted above.

At the same time, Martin, et al. disclose a therapeutic use of growth factors, to suppress intimal hyperplasia in situations where intimal hyperglasia arises when the endothelium is wholly or largely intact, and thus potentially capable of preventing or treating de novo stenosis. See page 1, lines 4-6 and page 4, lines 25-29. Therefore, Martin, et al. teach the inhibition of hyperplasia. See page 5, lines 14-19, and 24-28. In addition, Martin, et al. teach that VEGF agonists can be used in practicing their invention, and that a VEGF agonist functions like a VEGF and takes the place of VEGF. See

page 10, line 22 to page 13, line 17. While Carlyle et. al. teach that growth factors can promote cell growth, Martin, et al. find that VEGF and its agonists can suppress or treat de novo stenosis, another use for VEGF. Martin et. al. also do not teach dead bioprosthetic material lacking endothelium. Thus, there is no motivation to combine the teaching of Carlyle et. al. with that of Martin et. al. In addition, even if combined, the combination continues to teach VEGF and not stimulation compounds, the subject matter of claims 1 and 31.

Three criteria must be met to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference, or combination of references, must teach or suggest all the claim limitations. MPEP § 2142. Applicants respectfully traverse the rejection since the prior art fails to disclose all the claim limitations and there would be no motivation to combine the references as proposed by the Examiner, since the combined teaching does not teach or motivate stimulation compounds.

Dependent claims 2-30 and 32-35, which are dependent from independent claims 1 and 31, were also rejected under 35 U.S.C. §103(a) as being unpatentable over et. al. in view of Martin, et al. While Applicants do not acquiesce with the particular rejections to these dependent claims, it is believed that these rejections are moot in view of the remarks made in connection with independent claims 1 and 31. These dependent claims include all of the limitations of the base claim and any intervening claims, and

recite additional features which further distinguish these claims from the cited references. Therefore, dependent claims 2-30 and 32-35 are also in condition for allowance.

Applicants respectfully request withdrawal of the rejection of claims 1-35 under 35 U.S.C. § 103(a) as being anticipated by Carlyle, et al. in view of Martin, et al.

2. On page 5 of the Office Action, claims 3-7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Carlyle, et al. in view of Martin, et al. and further in view of Semenza, et al. (U.S. Patent Number 6,124,131) or Tsuzuki, et al. (Cancer Research. 60.2000).

The Examiner notes that neither Carlyle et. al. nor Martin et. al. specifically teach using HIF-Iα as the stimulator/agonist of VEGF, however the Examiner also notes that it would have been obvious at the time the invention was made to use HIF-Iα as the agonist as taught by Martin in the process of Carlyle because Semenza and Tsuzuki teach that HIF-Iα is a known agonist of VEGF. The Examiner asserts that there was a reasonable expectation that substituting HIF-Iα for the VEGF in the invention of Carlyle would produce like results. Accordingly, the Examiner contends that the claimed invention was prima facie obvious to one of ordinary skill in the art at the time the invention was made especially in the absence of evidence to the contrary.

Applicants respectfully traverse the rejections.

Applicants agree with the Examiner that neither Carlyle et. al. nor Martin et. al. specifically teach using HIF-Iα as the stimulator of VEGF, and that both Semenza and Tsuzuki et al. teach that HIF-Iα is a known agonist of VEGF. However, as noted in Martin, et al., a VEGF agonist functions like a VEGF and takes the place of VEGF.

Thus, an agonist is not a stimulation compound that stimulates the growth of VEGF, but only a VEGF look alike.

Further, Semenza teaches the discovery and isolation of unique variant forms of HIF-1α polypeptide that are stable under hypoxic and nonhypoxic conditions. See col. 2, lines 63-65. HIF-Iα polypeptide, when dimerized with HIF-1β, is a DNA binding protein, which is characterized as activating structural gene expression where the promoter region of the structural gene contains a HIF-1 binding site. See col. 5, lines 6-13. Examples of structural genes include erythropoietin (EPO), vascular endothelial growth hormone (VEGF) and glycolytic genes. See col. 5, lines 13-15. The HIF-Iα polypeptides can also be used to produce antibodies which are immunoreactive or selectively bind to epitopes of the sHIF-Iα polypeptides. An antibody which "selectively binds" to sHIF-Iα is an antibody that binds sHIF-Iα with a higher affinity the antibody binds to wild-type HIF-Iα. See col. 13, lines 25-30.

At the same time, Tsuzuki, et al. attempt to quantify the tumor activation of VEGF promoter in host stromal cells by implanting VEGF and wild-type embryonic stem cells in mice. See abstract. They teach that HIF-Iα binds to HRE of a target gene such as VEGF. See page 6248, col.1, Introduction. VEGF proteins bind to VEGF receptors on endothelia cells to mediate physiological function. See page 6248, col. 2, Introduction. While Carlyle et. al. teach that growth factors can promote cell growth, Martin, et al. find that VEGF and its agonists can also suppress or treat de novo stenosis. Semenza teaches the discovery and isolation of unique variant forms of HIF-1α, and Tsuzuki, et al. attempt to quantify the activation of VEGF promoter by implanting VEGF and stem cells in mice. There is no suggestion or motivation, either in the references themselves or in

the knowledge generally available to one of ordinary skill in the art, to modify Carlyle et. al. in view of Martin, et al. with Semenza or Tsuzuki, et al. to arrive at a medical device, such as an implantable medical device, a catheter, a dressing or a surgical instrument, having stimulation compounds that stimulates the production of VEGF, the subject matter of claim 1, as proposed by the Examiner. "(O)bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination. " *In re Bond*, 15 USPQ2d 1566, 1568 (Fed. Cir. 1990)(quoting *Carella v. Starlight Archery and Pro Line Co.*, 231 USPQ 644, 647 (Fed. Cir. 1986)). "[T]he mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." *In re Laskowski*, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989) (quoting *In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

In addition, the Examiner's suggestion of reasonable expectation of success is also not tenable since there is no motivation to combine the references, the three criteria to establish a *prima facie* case of obviousness, i.e. (1) that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference; (2) that there must be a reasonable expectation of success; and (3) that the prior art reference, or combination of references, must teach or suggest all the claim limitations, are not met. MPEP § 2142.

Therefore, claim 1 is not obvious over Carlyle, et al. in view of Martin, et al. and further in view of Semenza, et al. or Tsuzuki, et al.

Claims 3-7, which are dependent from independent claim 1, were rejected under 35 U.S.C. §103(a) as being unpatentable over Carlyle et. al. in view of Martin, et al. and further in view of Semenza, et al. (U.S. Patent Number 6,124,131) or Tsuzuki, et al. (Cancer Research. 60.2000). While Applicants do not acquiesce with the particular rejections to these dependent claims, it is believed that these rejections are moot in view of the remarks made in connection with independent claim 1. Therefore, dependent claims 2-30 and 32-35 are also in condition for allowance.

Applicants respectfully request withdrawal of the rejection of claims 3-7 under 35 U.S.C. § 103(a) as being anticipated by Carlyle, et al. in view of Martin, et al. and further in view of Semenza, et al. or Tsuzuki, et al.

III. Conclusion

In view of the amendments and reasons provided above, it is believed that all pending claims are in condition for allowance. Applicants respectfully request favorable reconsideration and early allowance of all pending claims.

If a telephone conference would be helpful in resolving any issues concerning this communication, please contact Applicants' attorney of record, Hallie A. Finucane at (952) 253-4134.

Respectfully submitted,

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Date: January 5, 2003

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